

Null Results in Brief

Tamoxifen Treatment in Danish Breast Cancer Patients and 5-Year Risk of Arterial Atherosclerotic Events: A Null Association

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Abstract

Although the effectiveness of tamoxifen in preventing the recurrence of breast cancer is well established, associations between tamoxifen and the occurrence of atherosclerotic events are not as clear. Breast cancer patients taking tamoxifen have lower serum cholesterol and other lipid levels than those not taking tamoxifen, suggesting that tamoxifen might prevent atherosclerotic events, but the existing studies are conflicting. We examined the relation between tamoxifen and incident hospitalization of angina pectoris, acute myocardial infarction, heart failure, and stroke. The study population of 16,289 women was identified from the Danish Breast Cancer Cooperative Group nationwide clinical database and

includes women diagnosed with stage I or II estrogen receptor-positive breast cancer between 1990 and 2004 at ages 45 to 69. Use of a large population-based sample with complete outcome ascertainment allowed us to calculate precise measures of risks, risk ratios, and adjusted hazard ratios comparing tamoxifen-treated patients with untreated patients. We found strong evidence for null associations for each of the four outcomes of interest during the first year and first 5 years after the start of therapy. These findings are important in risk/benefit analyses as tamoxifen therapy in postmenopausal women is being replaced with aromatase inhibitors. (Cancer Epidemiol Biomarkers Prev 2008;17(9):2509–11)

Introduction

Tamoxifen, a selective estrogen receptor modulator, effectively prevents breast cancer recurrence among women with estrogen-positive tumors (1). Tamoxifen treatment has also been associated with factors that may have a protective effect against atherosclerotic cardiovascular events such as reduced cholesterol (2), lipoprotein levels in postmenopausal women (3, 4), and inflammatory variables (5).

Despite this biomarker evidence suggesting that tamoxifen may prevent atherosclerotic manifestations, trials and nonrandomized studies have reported conflicting results. Some randomized trials have reported a protective effect of tamoxifen on mortality from myocardial infarction or coronary heart disease (6, 7), and others reported no association between tamoxifen and arterial outcomes, including stroke, myocardial infarction, and angina pectoris (8–10). Thus, whether tamoxifen is associated with arterial cardiovascular morbidity, and if so, to what extent, is not clear.

We therefore conducted a large population-based cohort study of breast cancer patients with long

follow-up and complete case ascertainment to assess the risk of angina pectoris, acute myocardial infarction, heart failure, and stroke as outcomes potentially prevented by tamoxifen treatment.

Materials and Methods

Study Population. Eligible women were diagnosed with International Union Against Cancer stage I or II estrogen receptor-positive breast cancer between 1990 and 2004 at ages 45 to 69, and reported to the Danish Breast Cancer Cooperative Group clinical database. We linked the study population database to the Danish National Registry of Patients covering all Danish acute care hospitals since 1977 to obtain information on cardiovascular outcomes (angina pectoris, myocardial infarction, heart failure, stroke) and comorbidities (see below), using each patient's central personal registry number. The central personal registry number is a unique identification number assigned to all Danish residents alive on April 1, 1968, born thereafter, or upon immigration (11). The Danish National Registry of Patients records the civil registration number of the patient, dates of admission and discharge, surgical procedure(s) done, and up to 20 diagnoses, classified according to ICD-8 codes for events occurring before 1994 and ICD-10 codes for all subsequent events. Outpatient and emergency room data have been

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Table 1. Arterial disease risks, risk ratios, and adjusted hazard ratios

	Tamoxifen treated (<i>n</i> = 8,232), no. of cases (risk %)	Tamoxifen untreated (<i>n</i> = 8,057), no. of cases (risk %)	Risk ratio (95% CI)	Adjusted hazard ratio (95% CI)*
Angina pectoris				
First year	18 (0.22)	16 (0.20)	1.1 (0.56-2.2)	1.2 (0.57-2.3)
First 5 years	79 (0.96)	104 (1.3)	0.74 (0.56-0.99)	0.88 (0.65-1.2)
Acute myocardial infarction				
First year	10 (0.12)	6 (0.07)	1.6 (0.59-4.5)	1.4 (0.52-4.0)
First 5 years	40 (0.49)	40 (0.50)	0.98 (0.63-1.5)	1.0 (0.67-1.6)
Heart failure				
First year	8 (0.10)	7 (0.09)	1.1 (0.41-3.1)	0.88 (0.32-2.4)
First 5 years	40 (0.49)	35 (0.43)	1.1 (0.71-1.8)	1.2 (0.77-1.9)
Stroke				
First year	20 (0.24)	23 (0.29)	0.85 (0.47-1.5)	0.81 (0.44-1.5)
First 5 years	84 (1.0)	87 (1.1)	0.95 (0.70-1.3)	1.0 (0.76-1.4)

*Adjusted for age group, diabetes, renal disease, hypertension, chronic obstructive pulmonary disease, radiation therapy, and chemotherapy.

available since 1994. End of follow-up was recorded as December 31, 2005.

Analysis. Tamoxifen treatment was classified as a dichotomous exposure using the prescribed Danish Breast Cancer Cooperative Group protocol after diagnosis of breast cancer. The tamoxifen-treated group was composed of women prescribed to any treatment that included tamoxifen, and the untreated group was defined as women on all other treatments that did not include tamoxifen. Arterial outcomes of interest were acute angina pectoris, myocardial infarction, heart failure, and stroke. Analyses were restricted to women with no recorded hospital diagnosis of existing cardiovascular diseases at the date of breast cancer surgery. The start of follow-up began 3 months after surgery date, which reflects an average duration between date of surgery and start of tamoxifen therapy.

Risks of events were analyzed individually for the first year and first 5 years after the start of follow-up. Risk ratios and 95% confidence intervals (CI) were computed as estimates of the association between tamoxifen therapy and incident cardiovascular disease using log-binomial regression (12). In addition, Cox proportional hazards analysis was used to compute adjusted hazard ratios (HR), with end of follow-up recorded as the date of the outcome of interest, death, or either 1 or 5 years after start of person-time contribution. In the analysis, we controlled for age, receipt of radiation therapy or chemotherapy, diabetes, renal disease, hypertension, and chronic obstructive pulmonary disease. The proportional hazards assumption was examined for each outcome by testing a model with the interaction between the exposure and the log of survival time as a covariate. The assumption of proportional hazards was satisfied for all models. All analyses were done using SAS version 9.

Results

After excluding 515 (3.0%) women with preexisting cardiovascular disease, 16 (0.09%) women who died before person-time start, and 262 (1.5%) women missing the prescribed protocol assignment, our final sample had 16,289 women. Demographic and health-related characteristics of the tamoxifen-treated (*n* = 8,232) and untreated (*n* = 8,057) women were examined for any differences; women taking tamoxifen were more likely to have their

breast cancer surgery in later years (60% during 2000-2004 versus 24% during 2000-2004) and were slightly older than unexposed women (mean age, 58 versus 56 years).

Table 1 shows the risks of the arterial atherosclerotic outcomes for both the tamoxifen-treated and untreated groups in the first year and first 5 years after the start of follow-up. All associations were near-null at all time points, with the exception of incident angina pectoris over the first 5 years (risk ratio, 0.74; 95% CI, 0.56-0.99). Further examination of the association between tamoxifen and the arterial outcomes reveals that when taking person-time and confounding factors into account, the association between tamoxifen and angina was no longer substantially protective during the 5-year risk period (adjusted hazard ratio, 0.88; 95% CI, 0.65-1.2). All remaining outcomes continued to show no association.

Discussion

Our large nationwide population study provides strong evidence for null associations between tamoxifen and subsequent risk of angina pectoris, acute myocardial infarction, heart failure, or stroke in the first 5 years after start of therapy. One earlier study reported a protective association between current tamoxifen and the occurrence of treated angina pectoris or myocardial infarction (odds ratio, 0.4; 95% CI, 0.2-0.7; ref. 13). However, this study compared breast cancer patients versus women with other cancers; our large cohort allowed comparison of breast cancer patients on tamoxifen with breast cancer patients not on tamoxifen. Our findings of no association have been reported previously in epidemiologic studies as well, specifically between tamoxifen and myocardial infarction or stroke (14, 15), although no large population-based cohort study has yet been presented.

Understanding the risk and benefit profile of tamoxifen therapy is increasingly critical because adjuvant tamoxifen is being replaced by aromatase inhibitors in postmenopausal breast cancer patients (16-18) and susceptibility to cardiovascular end points may be one consideration in choosing between the therapies (19). The validity of our findings depends ultimately on the quality of the hospital registry data. We had complete follow-up, and the coding of the diagnosis of acute myocardial infarction is very accurate (20) and slightly lower for stroke (21). Therefore, the high quality of our data and

large cohort show further evidence of no association, either protective or causal, between tamoxifen treatment and these four arterial outcomes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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BLOOD CANCER DISCOVERY

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